IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Fred S. Lamb et al.	Art Unit	: 1617
Serial No.	: 09/930,105	Examiner	: Jennifer M. Kim
Filed	: August 15, 2001	Docket	: 17023.017US1
Title	: USE OF CLC3 CHLORIDE CHANNEL BLOCKERS TO MODULATE VASCULAR TONE		

APPEAL BRIEF

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

The Final Office Action for this application was mailed September 12, 2006, and a Notice of Appeal was mailed March 12, 2007. Applicants respectfully appeal to the Board for review of the Examiner's final rejection.

This Appeal Brief is accompanied by a Petition, as well as the appropriate fee, to obtain a one-month extension for filing the Appeal Brief, thereby moving the deadline for response from May 16, 2007 to June 16, 2007. If necessary, please charge any additional fees or credit overpayment to Deposit Account 50-3503.

(1) Real Party in Interest

The real party in interest is the University of Iowa Research Foundation.

(2) Related Appeals and Interferences

None.

(3) Status of Claims

Claims 22-24, 27-29, 31-35, 38-43 stand finally rejected by the Examiner as noted in the Advisory Action mailed April 13, 2007. Claims 1-21, 25-26, 30 and 36-37 are canceled. The rejection of claims 22-24, 27-29, 31-35, and 38-43 is appealed.

"Express Mail" mailing label number: _____
Date of Deposit: _____
It is certified that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicates above and is addressed to Mail Stop Appeal Brief - Patent, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

(4) Status of Amendments

No amendment has been filed subsequent to the final rejection dated September 12, 2006.

(5) Summary of the Claimed Subject Matter

Claim 22

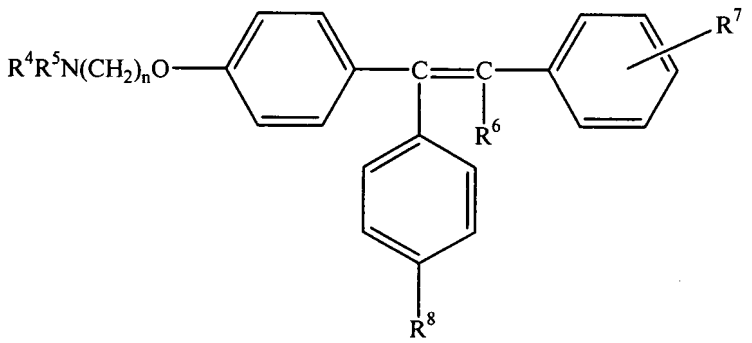
Claim 22 recites a method to modulate vascular tone in a male patient having compromised vascular tissue associated with erectile dysfunction, comprising administering to the male patient a pharmaceutically effective amount of a chloride channel blocking agent, or a pharmaceutically acceptable salt thereof.

Support for a method to modulate vascular tone of compromised vascular tissue associated with erectile dysfunction by administration of a chloride channel blocking agent is found in the specification at page 11, lines 16-19, and original claims 22 and 30.

Support for a "male patient" is found in the specification from page 1, line 18 through page 6, line 22, which sets forth the problem of male sexual dysfunction. Further, page 14, lines 7-9 indicates that the method treats male impotence. Applicant respectfully submits that one of ordinary skill in the art would recognize that if the patient has "compromised vascular tissue associated with erectile dysfunction" as recited in claim 22, then, logically, the patient is a male.

Claim 23

Claim 23 recites a method of claim 22, wherein the chloride channel blocking agent is a compound of Formula I



I

wherein either R^4 is H or a lower alkyl radical and R^5 is a lower alkyl radical, or R^4 and R^5 are joined together with the adjacent nitrogen atom to form a heterocyclic radical; R^6 is H or a lower

alkyl radical; R^7 is H, halo, OH, a lower alkyl radical, or is a buta-1,3-dienyl radical which together with the adjacent benzene ring forms a naphthyl radical; R^8 is H or OH; and n is 2; or a pharmaceutically acceptable salt thereof.

Claim 23 was not amended during prosecution; therefore, support for this claim is found in original claim 23. Support for Formula I is also found in the specification at page 12, lines 4-11.

Clam 24

Claim 24 recites a method of claim 23, wherein the compound is 1-p-β-dimethylaminoethoxyphenyl-trans-1,2-diphenylbut-1-ene, or a pharmaceutically acceptable salt thereof.

Support for 1-p-β-dimethylaminoethoxyphenyl-trans-1,2-diphenylbut-1-ene, or a pharmaceutically acceptable salt thereof is found in the specification at page 12, lines 9-11, and original claim 24.

Claim 27

Claim 27 recites a method of claim 22, wherein the chloride channel is a CLC3 channel.

Claim 27 was not amended during prosecution; therefore, support for this claim is found in original claim 27. Support for the feature of the chloride channel being a CLC3 channel is also found in the specification at page 13, lines 3-4.

Claim 28

Claim 28 recites the method of claim 27, wherein blocking the CLC3 channel results in diminished vasoconstriction to norepinephrine.

Claim 28 was not amended during prosecution; therefore, support for this claim is found in original claim 28. Support for the feature of the blocking of the CLC3 channel resulting in diminished vasoconstriction to norepinephrine is also found in the specification at page 13, lines 3-5.

Claim 29

Claim 29 recites the method of claim 22, wherein the agent modulates vascular tone by enhancing vasodilation.

Claim 29 was not amended during prosecution; therefore, support for this claim is found in original claim 29. Support for the feature of the agent modulating vacular tone by enhancing vasodilation is also found in the specification at page 13, lines 5-7.

Claim 31

Claim 31 recites the method of claim 22, further comprising administering a pharmaceutically effective compound selected from an anti-diabetes agent, an anti-hypertension agent, an anti-coronary artery disease agent, an anti-restenosis agent, and a vasodilatory agent.

Support for the feature of additionally administering an anti-diabetes agent, an anti-hypertension agent, an anti-coronary artery disease agent, an anti-restenosis agent, and a vasodilatory agent is found in the specification at page 9, lines 2-5; page 12, line 20 to page 13, line 2 and original claim 31.

Claim 32

Claim 32 recites a method of claim 22, wherein the agent is administered intravenously or orally.

Claim 32 was not amended during prosecution; therefore, support for this claim is found in original claim 32. Support for the agent being administered intravenously or orally is also found in the specification at page 12, lines 20-21.

Claim 33

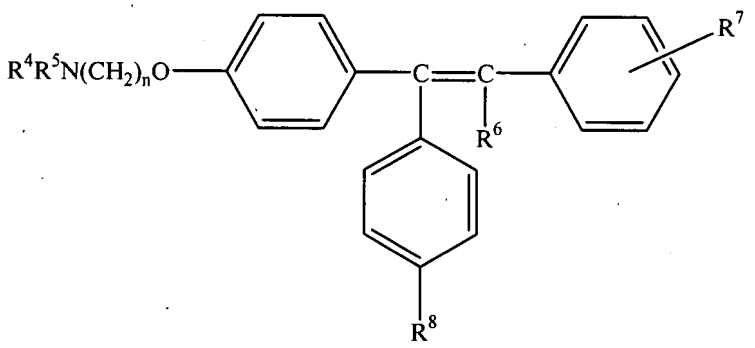
Claim 33 recites a method to modulate penile vascular tone in a male mammal in need thereof, said method comprising administering a pharmaceutically effective amount of a chloride channel blocking agent, or a pharmaceutically acceptable salt thereof.

Support for "modulate penile vascular tone in a mammal" involving "administering a pharmaceutically effective amount of a chloride channel blocking agent, or a pharmaceutically acceptable salt thereof" is found in the specification at page 13, lines 8-10. Support for a "male"

is found in the specification from page 1, line 18 through page 6, line 22, which sets forth the problem of male sexual dysfunction. Applicant respectfully submits that one of ordinary skill in the art would recognize that if the method is to modulate penile vascular tone in a mammal as recited in claim 33, then, logically, the patient is a male.

Claim 34

Claim 34 recites a method of claim 33, wherein the chloride channel blocking agent is a compound of Formula I



I

wherein either R^4 is H or a lower alkyl radical and R^5 is a lower alkyl radical, or R^4 and R^5 are joined together with the adjacent nitrogen atom to form a heterocyclic radical; R^6 is H or a lower alkyl radical; R^7 is H, halo, OH, a lower alkyl radical, or is a buta-1,3-dienyl radical which together with the adjacent benzene ring forms a naphthyl radical; R^8 is H or OH; and n is 2; or a pharmaceutically acceptable salt thereof.

Claim 34 was not amended during prosecution; therefore, support for this claim is found in original claim 34. Support for a method to modulate penile vascular tone in a mammal comprising administering a pharmaceutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof is found at page 13, lines 8-16.

Claim 35

Claim 35 recites the method of claim 34, wherein the compound administered is 1-p-β-dimethylaminoethoxyphenyl-trans-l, 2-diphenylbut-1-ene, or a pharmaceutically acceptable salt thereof.

Support for the used of 1-p-β-dimethylaminoethoxyphenyl-trans-l, 2-diphenylbut-1-ene, which is also called tamoxifen, can be found in the specification at page 13, lines 15-16, and in original claim 35.

Claim 38

Claim 38 recites the method of claim 33, wherein the agent is administered orally or intravenously.

Claim 38 was not amended during prosecution; therefore, support for this claim is found in original claim 38. Support for the agent being administered orally or intravenously is found at page 14, lines 1-3.

Claim 39

Claim 39 recites a method of claim 33, wherein the chloride channel is a CLC3 channel.

Claim 39 was not amended during prosecution; therefore, support for this claim is found in original claim 39. Support for the chloride channel being a CLC3 channel is found at page 14, lines 4-6.

Claim 40

Claim 40 recites the method of claim 39, wherein blocking the CLC3 channel results in diminished vasoconstriction to norepinephrine.

Claim 40 was not amended during prosecution; therefore, support for this claim is found in original claim 40. Support for the blocking of the CLC3 channel resulting in diminished vasoconstriction to norepinephrine is found at page 14, lines 4-6.

Claim 41

Claim 41 recites the method of claim 39, wherein blocking the CLC3 channel reduces penile sympathetic tone.

Claim 41 was not amended during prosecution; therefore, support for this claim is found in original claim 41. Support for the blocking of the CLC3 channel reducing penile sympathetic tone is found at page 14, lines 4-6.

Claim 42

Claim 42 recites the method of claim 41, wherein the reduction of penile sympathetic tone induces an erection.

Claim 42 was not amended during prosecution; therefore, support for this claim is found in original claim 42. Support for the reduction of penile sympathetic tone inducing an erection is found at page 14, lines 4-6.

Claim 43

Claim 43 recites a method for treating erectile dysfunction in a male patient comprising administering to the male patient a composition comprising a CLC3 channel blocking agent or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Support for "method for treating erectile dysfunction in a patient comprising administering to the patient a composition comprising a CLC3 channel blocking agent or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier" is found in original claim 43.

Support for a "male" is found in the specification from page 1, line 18 through page 6, line 22, which sets forth the problem of male sexual dysfunction. Further, page 14, lines 7-9 indicates that the method treats male impotence. Applicant respectfully submits that one of ordinary skill in the art would recognize that if the patient has "compromised vascular tissue associated with erectile dysfunction" as recited in claim 22, then, logically, the patient is a male.

(6) Grounds of Rejection to Be Reviewed on Appeal

The issues being appealed are the following:

(1) Whether claims 22-24, 27-29, 33-35 or 39-43 are anticipated under 35 U.S.C. § 102(b) by Delaney *et al.* (Delaney *et al.*, (1996) *The Breast* 5:53-54) as evidenced by U.S. Patent No. 5,658,936 (the Kifor *et al.* patent); and

(2) Whether claims 31, 32 or 38 are unpatentable under 35 U.S.C. § 103(a) over Delaney *et al.* (Delaney *et al.*, (1996) *The Breast* 5:53-54) in view of U.S. Patent No. 6,266,560 (the Zhang *et al.* patent) and *Drug Facts and Comparisons* (1997).

(7) Argument

A. The Claims Are Distinguishable over Delaney *et al.*

The Examiner alleges that claims 22-24, 27-29, 33-35 and 39-43 are anticipated by Delaney *et al.* (Delaney *et al.*, (1996) *The Breast* 5:53-54) as evidenced by the Kifor *et al.* patent (U.S. Patent No. 5,658,936).

The Examiner stated that Delaney *et al.* teaches that a patient treated with tamoxifen exhibited significantly enhanced libido. The Examiner also stated that the Kifor *et al.* patent provides evidence of the equivalence between improvement in erectile function and increased libido. The Examiner further stated that Applicants' recitation in the claims of a mechanism for modulating penile vascular tone does not represent a patentable limitation, and that tamoxifen has been previously used to obtain the same pharmacological effect (enhanced erection) that would result from the claimed method.

Claim 22

Independent claim 22 recites a method to modulate vascular tone in a male patient having compromised vascular tissue associated with erectile dysfunction, comprising administering to the male patient a pharmaceutically effective amount of a chloride channel blocking agent, or a pharmaceutically acceptable salt thereof.

Applicant respectfully submits that Delaney *et al.* do not teach the method of claim 22 and therefore fail to anticipate claim 22. Delaney *et al.* disclose that one male patient on a tamoxifen regimen had experienced increased libido during his course of treatment. At no point do Delaney *et al.* disclose that the patient had compromised vascular tissue associated with erectile dysfunction, as recited in claim 22. While Delaney *et al.* suggests that tamoxifen may have been the cause of the patient's increased libido, Delaney *et al.* fails to even suggest that tamoxifen might be useful to modulate penile vascular tone in a patient with erectile dysfunction.

Page 4 of the September 12, 2006 Office Action states that "the patient being treated by Delaney *et al.* had **enhanced** libido upon administration of tamoxifen" (emphasis in original), but then later states that "when tamoxifen treatment was continued, the libido condition was returned to normal." These two statements are inconsistent. The Office Action first states that the tamoxifen treatment was the causative agent to increase the patient's libido, but later states that the tamoxifen treatment caused the patient's libido to reduce back down to a normal level.

The Delaney *et al.* article states that the increased libido was a negative complication of the tamoxifen treatment, as indicated by the statement that the patient "complained of two side-effects since the commencement of tamoxifen – the development of an acneform rash and for the immediately preceding 6 months significantly enhanced libido" (page 53, first column). There is no support in Delaney *et al.* for the statement on page 5 of the Office Action that "Delaney et al. continued tamoxifen in the patient while the patient was suffering from enhanced libido, to decrease the enhanced libido condition in the patient back to normal" (emphasis added).

Applicant asserts that Delaney *et al.* do not show a correlation between the administration of tamoxifen to the patient and the observed increase in libido in the patient. As discussed previously, the Delaney *et al.* reference discusses a case history of one male patient with metastatic breast cancer. The sequence of events was as follows:

Date	**Activity**
October 1988	Surgery for carcinoma
June 1992	Multiple bone metastases
February 1993	Radiotherapy
April 1993	Tamoxifen treatment started
August 1993	Side-effects began (significantly enhanced libido, rash)
February 1994	Patient seen for review, reported side-effects
January 1995	Patient re-evaluated, reported cessation of side-effects even though continued tamoxifen treatment (libido returned to normal, rash resolved)

Thus, during the middle portion of the period when he was treated with tamoxifen, he experienced increased libido. According to Delaney *et al.*, the patient began tamoxifen treatment in April of 1993. Ten months later, in February of 1994, he reported that he had experienced significantly enhanced libido for the immediately preceding six months. It is important to note that the onset of increased libido did not occur until the patient had been taking tamoxifen for

about four months. Moreover, when the patient was reevaluated in January of 1995, his libido had returned to normal levels (and the other negative side effect of the rash resolved) despite the fact that he continued tamoxifen treatment. In other words, the patient's increased libido was not observed until the patient had been on tamoxifen for a several months, and it resolved before the patient discontinued his tamoxifen treatment.

Applicant asserts that there is a lack of causation (*i.e.*, a cause-and-effect relation) between the administration of tamoxifen and the effect observed by Delaney *et al.* Applicant asserts that Delaney *et al.* do not show a correlation between the administration of tamoxifen to the patient and the observed increase in libido in the patient. The patient's increased libido was not observed until the patient had been on tamoxifen for a several months, and it resolved before the patient discontinued his tamoxifen treatment. Thus, Delaney *et al.* merely discloses that one male breast cancer patient on a tamoxifen regimen had experienced an increased libido during the course of treatment, and that the period of time in which he had an increased libido was not co-extensive with the period of time in which he was administered tamoxifen.

Delaney *et al.* do not report that any studies were conducted to determine whether the tamoxifen treatment was definitively linked to the patient's increase in libido. In addition, Delaney *et al.* did not attempt to establish whether the increased libido might have been linked to any of the other treatments to which the cancer patient had been subjected, including chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil, as well as radiotherapy. In fact, the authors of Delaney *et al.* were unsure as to the cause of the increased libido, as they speculate that it may have been related to the relatively young age of the patient. They do not disclose any evidence that tamoxifen treatment and increased libido were causatively linked.

In addition, Delaney *et al.* disclose that the increase in libido observed in this one patient was contrary to other case reports in which tamoxifen therapy was associated with impotence. In fact, Delaney *et al.* disclose that previous studies had found that 5 to 30 percent of men receiving tamoxifen experienced reduced libido. Thus, Delaney *et al.* clearly teach that the patient in question was an outlier, and that tamoxifen treatment would be expected to reduce libido rather than to increase libido.

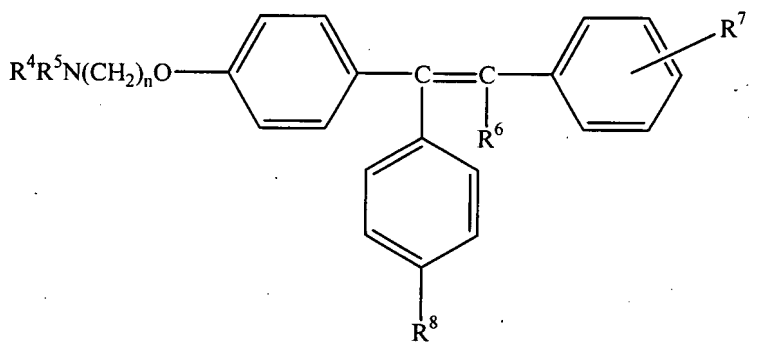
Moreover, libido and erectile dysfunction are significantly different conditions; an improvement in erectile function cannot be equated with an increase in libido. Libido is a psychological phenomenon that is defined by the Merriam-Webster online dictionary as "emotional or psychic energy that in psychoanalytic theory is derived from primitive biological urges and that is usually goal-directed; or sexual drive." Erectile dysfunction is a physiological condition that is defined by the On-Line Medical Dictionary as "a consistent inability to sustain an erection sufficient for sexual intercourse." Given these differences, increasing libido and modulating penile vascular tone to treat erectile dysfunction are likely accomplished by different mechanisms. Thus, even if tamoxifen treatment was casually linked to the psychological condition of an increased libido, there would have been no reason to believe that it could be used to physiologically modulate penile vascular tone or to treat erectile dysfunction.

The Kifor *et al.* patent is consistent with the above definitions when it states that improved erectile function can include "any enhancement of the ability of a subject to maintain an erection, induce or improve ejaculation, induce or improve orgasm, and increase libido." (*See*, column 7, lines 4-8 of the Kifor *et al.* patent.) Thus, an increase in libido may improve erectile dysfunction, but does not necessarily do so. As such, improved erectile function and increased libido are distinct and cannot be equated.

In summary, given the differences between libido and erectile dysfunction, together with the lack of evidence establishing that tamoxifen treatment was causally associated with one individual's increased libido, as well as the failure of Delaney *et al.* to disclose that tamoxifen would be useful in a patient having compromised vascular tissue and/or erectile dysfunction, it is clear that the cited documents does not anticipate claim 22.

Claim 23

Claim 23 recites the method of claim 22 (*i.e.*, a method to modulate vascular tone in a male patient having compromised vascular tissue associated with erectile dysfunction, comprising administering to the male patient a pharmaceutically effective amount of a chloride channel blocking agent, or a pharmaceutically acceptable salt thereof), wherein the chloride channel blocking agent is a compound of Formula I:



I

wherein either R^4 is H or a lower alkyl radical and R^5 is a lower alkyl radical, or R^4 and R^5 are joined together with the adjacent nitrogen atom to form a heterocyclic radical; R^6 is H or a lower alkyl radical; R^7 is H, halo, OH, a lower alkyl radical, or is a buta-1,3-dienyl radical which together with the adjacent benzene ring forms a naphthyl radical; R^8 is H or OH; and n is 2; or a pharmaceutically acceptable salt thereof.

Applicants respectfully assert that Delaney *et al.* fail to anticipate claim 23. As discussed above, Delaney *et al.* disclose that one male patient on a tamoxifen regimen had experienced increased libido during a portion of his course of treatment. At no point do Delaney *et al.* disclose that the patient had compromised vascular tissue associated with erectile dysfunction, as recited in claim 23. As discussed above, Delaney *et al.* fails to suggest that tamoxifen might be useful to modulate penile vascular tone in a patient with erectile dysfunction. Further, as discussed above, Delaney *et al.* fail to establish a causative link between tamoxifen treatment and increased libido.

Delaney *et al.* disclose that one male cancer patient experienced increased libido during a course of treatment with tamoxifen. According to Delaney *et al.*, the patient began tamoxifen treatment in April of 1993. Ten months later, in February of 1994, he reported that he had experienced significantly enhanced libido for the immediately preceding six months. As such, the onset of increased libido did not occur until the patient had been taking tamoxifen for about four months. Moreover, when the patient was reevaluated in January of 1995, his libido had returned to normal levels despite the fact that he continued tamoxifen treatment. Thus, the perceived side effect of increased libido was not observed until the patient had been on tamoxifen for a relatively long time, and it resolved before the patient discontinued his tamoxifen treatment.

Further, as discussed above, Delaney *et al.* do not report that any studies were conducted to determine whether the tamoxifen treatment was definitively linked to the patient's increase in libido, and did not attempt to establish whether the increased libido might have been linked to any of the other treatments to which the cancer patient had been subjected, including chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil, as well as radiotherapy. Instead, the authors of Delaney *et al.* were unsure as to the cause of the increased libido. They do not disclose any evidence that tamoxifen treatment and increased libido were causatively linked.

In addition, as discussed above, Delaney *et al.* disclose that the increase in libido observed in this one patient was contrary to other case reports in which tamoxifen therapy was associated with impotence, and that previous studies had found that 5 to 30 percent of men receiving tamoxifen experienced reduced libido. Thus, Delaney *et al.* clearly teaches that the patient in question was an outlier, and that tamoxifen treatment would be expected to reduce libido rather than to increase libido.

Moreover, as discussed above, libido and erectile dysfunction are significantly different conditions; an improvement in erectile function cannot be equated with an increase in libido. Thus, even if tamoxifen treatment was casually linked to increased libido, there would have been no reason to believe that it could be used to modulate penile vascular tone or to treat erectile dysfunction. Improved erectile function and increased libido are distinct and cannot be equated.

In summary, given the differences between libido and erectile dysfunction, together with the lack of evidence establishing that tamoxifen treatment was causally associated with one individual patient's increased libido, as well as the failure of Delaney *et al.* to disclose that tamoxifen would be useful in a patient having compromised vascular tissue and/or erectile dysfunction, it is clear that the cited documents do not anticipate claim 23.

Claim 24

Claim 24 recites a method of claim 23 (*i.e.*, a method to modulate vascular tone in a male patient having compromised vascular tissue associated with erectile dysfunction, comprising administering to the male patient a pharmaceutically effective amount of a chloride channel blocking agent, or a pharmaceutically acceptable salt thereof, wherein the chloride channel

blocking agent is a compound of Formula I), wherein the compound is 1-p-β-dimethylaminoethoxyphenyl-trans-1,2-diphenylbut-1-ene, or a pharmaceutically acceptable salt thereof. The compound 1-p-β-dimethylaminoethoxyphenyl-trans-1,2-diphenylbut-1-ene is also commonly called tamoxifen.

Applicants respectfully assert that Delaney *et al.* fails to anticipate claim 24. As discussed above, Delaney *et al.* discloses that one male patient on a tamoxifen regimen had experienced increased libido during a portion of his course of treatment. At no point do Delaney *et al.* disclose that the patient had compromised vascular tissue associated with erectile dysfunction, as recited in claim 24. As discussed above, Delaney *et al.* fails to suggest that tamoxifen might be useful to modulate penile vascular tone in a patient with erectile dysfunction. Further, as discussed above, Delaney *et al.* fail to establish a causative link between tamoxifen treatment and increased libido.

Delaney *et al.* disclose that one male cancer patient experienced increased libido during a course of treatment with tamoxifen. According to Delaney *et al.*, the patient began tamoxifen treatment in April of 1993. Ten months later, in February of 1994, he reported that he had experienced significantly enhanced libido for the immediately preceding six months. As such, the onset of increased libido did not occur until the patient had been taking tamoxifen for about four months. Moreover, when the patient was reevaluated in January of 1995, his libido had returned to normal levels despite the fact that he continued tamoxifen treatment. Thus, the perceived side effect of increased libido was not observed until the patient had been on tamoxifen for a relatively long time, and it resolved before the patient discontinued his tamoxifen treatment.

Further, as discussed above, Delaney *et al.* do not report that any studies were conducted to determine whether the tamoxifen treatment was definitively linked to the patient's increase in libido, and did not attempt to establish whether the increased libido might have been linked to any of the other treatments to which the cancer patient had been subjected, including chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil, as well as radiotherapy. Instead, the authors of Delaney *et al.* were unsure as to the cause of the increased libido. They do not disclose any evidence that tamoxifen treatment and increased libido were causatively linked.

In addition, as discussed above, Delaney *et al.* disclose that the increase in libido observed in this one patient was contrary to other case reports in which tamoxifen therapy was associated with impotence, and that previous studies had found that 5 to 30 percent of men receiving tamoxifen experienced reduced libido. Thus, Delaney *et al.* clearly teaches that the patient in question was an outlier, and that tamoxifen treatment would be expected to reduce libido rather than to increase libido.

Moreover, as discussed above, libido and erectile dysfunction are significantly different conditions; an improvement in erectile function cannot be equated with an increase in libido. Thus, even if tamoxifen treatment was casually linked to increased libido, there would have been no reason to believe that it could be used to modulate penile vascular tone or to treat erectile dysfunction. Improved erectile function and increased libido are distinct and cannot be equated.

In summary, given the differences between libido and erectile dysfunction, together with the lack of evidence establishing that tamoxifen treatment was causally associated with one individual's increased libido, as well as the failure of Delaney *et al.* to disclose that tamoxifen would be useful in a patient having compromised vascular tissue and/or erectile dysfunction, it is clear that the cited documents do not anticipate claim 24.

Claim 27

Claim 27 recites a method of claim 22 (*i.e.*, a method to modulate vascular tone in a male patient having compromised vascular tissue associated with erectile dysfunction, comprising administering to the male patient a pharmaceutically effective amount of a chloride channel blocking agent, or a pharmaceutically acceptable salt thereof), wherein the chloride channel is a CLC3 channel.

Applicants respectfully assert that Delaney *et al.* fails to anticipate claim 27. As discussed above, Delaney *et al.* discloses that one male patient on a tamoxifen regimen had experienced increased libido during a portion of his course of treatment. At no point do Delaney *et al.* disclose that the patient had compromised vascular tissue associated with erectile dysfunction, as recited in claim 27. Delaney *et al.* fails to suggest that a chloride channel blocking agent might be useful to modulate penile vascular tone in a patient with erectile

dysfunction. Further, Delaney *et al.* fail to establish a causative link between the use of a chloride channel blocking agent and increased libido.

Delaney *et al.* disclose that one male cancer patient experienced increased libido during a course of treatment with tamoxifen. According to Delaney *et al.*, the patient began tamoxifen treatment in April of 1993. Ten months later, in February of 1994, he reported that he had experienced significantly enhanced libido for the immediately preceding six months. As such, the onset of increased libido did not occur until the patient had been taking tamoxifen for about four months. Moreover, when the patient was reevaluated in January of 1995, his libido had returned to normal levels despite the fact that he continued tamoxifen treatment. Thus, the perceived side effect of increased libido was not observed until the patient had been on tamoxifen for a relatively long time, and it resolved before the patient discontinued his tamoxifen treatment.

Further, Delaney *et al.* do not report that any studies were conducted to determine whether the tamoxifen treatment was definitively linked to the patient's increase in libido, and did not attempt to establish whether the increased libido might have been linked to any of the other treatments to which the cancer patient had been subjected, including chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil, as well as radiotherapy. Instead, the authors of Delaney *et al.* were unsure as to the cause of the increased libido. They do not disclose any evidence that tamoxifen treatment and increased libido were causatively linked.

In addition, as discussed above, Delaney *et al.* disclose that the increase in libido observed in this one patient was contrary to other case reports in which tamoxifen therapy was associated with impotence, and that previous studies had found that 5 to 30 percent of men receiving tamoxifen experienced reduced libido. Thus, Delaney *et al.* clearly teaches that the patient in question was an outlier, and that tamoxifen treatment would be expected to reduce libido rather than to increase libido.

Moreover, as discussed above, libido and erectile dysfunction are significantly different conditions; an improvement in erectile function cannot be equated with an increase in libido. Thus, even if tamoxifen treatment was casually linked to increased libido, there would have been no reason to believe that it could be used to modulate penile vascular tone or to treat erectile dysfunction. Improved erectile function and increased libido are distinct and cannot be equated.

In summary, given the lack of evidence establishing that tamoxifen treatment was causally associated with one individual's increased libido, as well as the failure of Delaney *et al.* to disclose that a chloride channel blocking agent would be useful in a patient having compromised vascular tissue and/or erectile dysfunction, it is clear that the cited documents do not anticipate claim 27.

Claim 28

Claim 28 recites the method of claim 27 (*i.e.*, a method to modulate vascular tone in a male patient having compromised vascular tissue associated with erectile dysfunction, comprising administering to the male patient a pharmaceutically effective amount of a chloride channel blocking agent, or a pharmaceutically acceptable salt thereof, wherein the chloride channel is a CLC3 channel), wherein blocking the CLC3 channel results in diminished vasoconstriction to norepinephrine.

Applicants respectfully assert that Delaney *et al.* fails to anticipate claim 28. As discussed above, Delaney *et al.* discloses that one male patient on a tamoxifen regimen had experienced increased libido during a portion of his course of treatment. At no point do Delaney *et al.* disclose that the patient had compromised vascular tissue associated with erectile dysfunction, as recited in claim 28. Delaney *et al.* fails to suggest that tamoxifen might be useful to modulate penile vascular tone in a patient with erectile dysfunction, wherein blocking a CLC3 channel results in diminished vasoconstriction to norepinephrine. Further, Delaney *et al.* fail to establish a causative link between tamoxifen treatment and increased libido.

Delaney *et al.* disclose that one male cancer patient experienced increased libido during a course of treatment with tamoxifen. According to Delaney *et al.*, the patient began tamoxifen treatment in April of 1993. Ten months later, in February of 1994, he reported that he had experienced significantly enhanced libido for the immediately preceding six months. As such, the onset of increased libido did not occur until the patient had been taking tamoxifen for about four months. Moreover, when the patient was reevaluated in January of 1995, his libido had returned to normal levels despite the fact that he continued tamoxifen treatment. Thus, the perceived side effect of increased libido was not observed until the patient had been on

tamoxifen for a relatively long time, and it resolved before the patient discontinued his tamoxifen treatment.

Further, as discussed above, Delaney *et al.* do not report that any studies were conducted to determine whether the tamoxifen treatment was definitively linked to the patient's increase in libido, and did not attempt to establish whether the increased libido might have been linked to any of the other treatments to which the cancer patient had been subjected, including chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil, as well as radiotherapy. Instead, the authors of Delaney *et al.* were unsure as to the cause of the increased libido. They do not disclose any evidence that tamoxifen treatment and increased libido were causatively linked.

In addition, as discussed above, Delaney *et al.* disclose that the increase in libido observed in this one patient was contrary to other case reports in which tamoxifen therapy was associated with impotence, and that previous studies had found that 5 to 30 percent of men receiving tamoxifen experienced reduced libido. Thus, Delaney *et al.* clearly teaches that the patient in question was an outlier, and that tamoxifen treatment would be expected to reduce libido rather than to increase libido.

Moreover, as discussed above, libido and erectile dysfunction are significantly different conditions; an improvement in erectile function cannot be equated with an increase in libido. Thus, even if tamoxifen treatment was casually linked to increased libido, there would have been no reason to believe that it could be used to modulate penile vascular tone or to treat erectile dysfunction. Improved erectile function and increased libido are distinct and cannot be equated.

In summary, given the differences between libido and erectile dysfunction, together with the lack of evidence establishing that tamoxifen treatment was causally associated with one individual's increased libido, as well as the failure of Delaney *et al.* to disclose that tamoxifen would be useful in a patient having compromised vascular tissue and/or erectile dysfunction, it is clear that the cited documents do not anticipate claim 28.

Claim 29

Claim 29 recites the method of claim 22 (*i.e.*, a method to modulate vascular tone in a male patient having compromised vascular tissue associated with erectile dysfunction,

comprising administering to the male patient a pharmaceutically effective amount of a chloride channel blocking agent, or a pharmaceutically acceptable salt thereof), wherein the agent modulates vascular tone by enhancing vasodilation.

Applicants respectfully assert that Delaney *et al.* fails to anticipate claim 29. As discussed above, Delaney *et al.* discloses that one male patient on a tamoxifen regimen had experienced increased libido during a portion of his course of treatment. At no point do Delaney *et al.* disclose that the patient had compromised vascular tissue associated with erectile dysfunction or that a chloride channel blocking agent modulates vascular tone by enhancing vasodilation, as recited in claim 29. Delaney *et al.* fails to suggest that tamoxifen might be useful to modulate penile vascular tone in a patient with erectile dysfunction. Further, Delaney *et al.* fail to establish a causative link between tamoxifen treatment and increased libido.

Delaney *et al.* disclose that one male cancer patient experienced increased libido during a course of treatment with tamoxifen. According to Delaney *et al.*, the patient began tamoxifen treatment in April of 1993. Ten months later, in February of 1994, he reported that he had experienced significantly enhanced libido for the immediately preceding six months. As such, the onset of increased libido did not occur until the patient had been taking tamoxifen for about four months. Moreover, when the patient was reevaluated in January of 1995, his libido had returned to normal levels despite the fact that he continued tamoxifen treatment. Thus, the perceived side effect of increased libido was not observed until the patient had been on tamoxifen for a relatively long time, and it resolved before the patient discontinued his tamoxifen treatment.

Further, as discussed above, Delaney *et al.* do not report that any studies were conducted to determine whether the tamoxifen treatment was definitively linked to the patient's increase in libido, and did not attempt to establish whether the increased libido might have been linked to any of the other treatments to which the cancer patient had been subjected, including chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil, as well as radiotherapy. Instead, the authors of Delaney *et al.* were unsure as to the cause of the increased libido. They do not disclose any evidence that tamoxifen treatment and increased libido were causatively linked.

In addition, as discussed above, Delaney *et al.* disclose that the increase in libido observed in this one patient was contrary to other case reports in which tamoxifen therapy was associated with impotence, and that previous studies had found that 5 to 30 percent of men receiving tamoxifen experienced reduced libido. Thus, Delaney *et al.* clearly teaches that the patient in question was an outlier, and that tamoxifen treatment would be expected to reduce libido rather than to increase libido.

Moreover, as discussed above, libido and erectile dysfunction are significantly different conditions; an improvement in erectile function cannot be equated with an increase in libido. Thus, even if tamoxifen treatment was casually linked to increased libido, there would have been no reason to believe that it could be used to modulate penile vascular tone or to treat erectile dysfunction. Improved erectile function and increased libido are distinct and cannot be equated.

In summary, given the differences between libido and erectile dysfunction, together with the lack of evidence establishing that tamoxifen treatment was causally associated with one individual's increased libido, as well as the failure of Delaney *et al.* to disclose that tamoxifen would be useful in a patient having compromised vascular tissue and/or erectile dysfunction, it is clear that the cited documents do not anticipate claim 29.

Claim 33

Independent claim 33 recites a method to modulate penile vascular tone in a male mammal in need thereof, said method comprising administering a pharmaceutically effective amount of a chloride channel blocking agent, or a pharmaceutically acceptable salt thereof.

Applicants respectfully assert that Delaney *et al.* fails to anticipate claim 33. As discussed above, Delaney *et al.* discloses that one male patient on a tamoxifen regimen had experienced increased libido during a portion of his course of treatment. At no point do Delaney *et al.* disclose that the patient had a need for the modulation of penile vascular tone, as recited in claim 33. Delaney *et al.* fails to suggest that tamoxifen might be useful to modulate penile vascular tone in a patient in need thereof. Further, as discussed above, Delaney *et al.* fail to establish a causative link between tamoxifen treatment and increased libido.

Delaney *et al.* disclose that one male cancer patient experienced increased libido during a course of treatment with tamoxifen. According to Delaney *et al.*, the patient began tamoxifen

treatment in April of 1993. Ten months later, in February of 1994, he reported that he had experienced significantly enhanced libido for the immediately preceding six months. As such, the onset of increased libido did not occur until the patient had been taking tamoxifen for about four months. Moreover, when the patient was reevaluated in January of 1995, his libido had returned to normal levels despite the fact that he continued tamoxifen treatment. Thus, the perceived side effect of increased libido was not observed until the patient had been on tamoxifen for a relatively long time, and it resolved before the patient discontinued his tamoxifen treatment.

Further, as discussed above, Delaney *et al.* do not report that any studies were conducted to determine whether the tamoxifen treatment was definitively linked to the patient's increase in libido, and did not attempt to establish whether the increased libido might have been linked to any of the other treatments to which the cancer patient had been subjected, including chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil, as well as radiotherapy. Instead, the authors of Delaney *et al.* were unsure as to the cause of the increased libido. They do not disclose any evidence that tamoxifen treatment and increased libido were causatively linked.

In addition, as discussed above, Delaney *et al.* disclose that the increase in libido observed in this one patient was contrary to other case reports in which tamoxifen therapy was associated with impotence, and that previous studies had found that 5 to 30 percent of men receiving tamoxifen experienced reduced libido. Thus, Delaney *et al.* clearly teaches that the patient in question was an outlier, and that tamoxifen treatment would be expected to reduce libido rather than to increase libido.

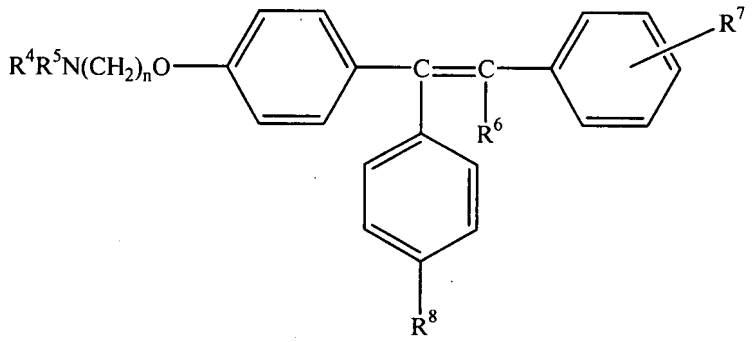
Moreover, libido and modulation of penile vascular tone are significantly different conditions; a modulation in penile vascular tone cannot be equated with an increase in libido. Thus, even if tamoxifen treatment was casually linked to increased libido, there would have been no reason to believe that it could be used to modulate penile vascular tone. Modulated penile vascular tone and increased libido are distinct and cannot be equated.

In summary, given the differences between libido and the modulation of penile vascular tone, together with the lack of evidence establishing that tamoxifen treatment was causally associated with one individual's increased libido, as well as the failure of Delaney *et al.* to

disclose that tamoxifen would be useful in a patient in need of the modulation of penile vascular tone, it is clear that the cited documents do not anticipate claim 33.

Claim 34

Claim 34 recites a method of claim 33 (*i.e.*, a method to modulate penile vascular tone in a male mammal in need thereof, said method comprising administering a pharmaceutically effective amount of a chloride channel blocking agent, or a pharmaceutically acceptable salt thereof), wherein the chloride channel blocking agent is a compound of Formula I



I

wherein either R^4 is H or a lower alkyl radical and R^5 is a lower alkyl radical, or R^4 and R^5 are joined together with the adjacent nitrogen atom to form a heterocyclic radical; R^6 is H or a lower alkyl radical; R^7 is H, halo, OH, a lower alkyl radical, or is a buta-1,3-dienyl radical which together with the adjacent benzene ring forms a naphthyl radical; R^8 is H or OH; and n is 2; or a pharmaceutically acceptable salt thereof.

Applicants respectfully assert that Delaney *et al.* fails to anticipate claim 34. As discussed above, Delaney *et al.* discloses that one male patient on a tamoxifen regimen had experienced increased libido during a portion of his course of treatment. At no point do Delaney *et al.* disclose that the patient had a need for the modulation of penile vascular tone, as recited in claim 34.

Delaney *et al.* fails to suggest that tamoxifen might be useful to modulate penile vascular tone in a patient in need thereof. Further, as discussed above, Delaney *et al.* fail to establish a causative link between tamoxifen treatment and increased libido. Delaney *et al.* disclose that one male cancer patient experienced increased libido during a course of treatment with tamoxifen. According to Delaney *et al.*, the patient began tamoxifen treatment in April of 1993. Ten months

later, in February of 1994, he reported that he had experienced significantly enhanced libido for the immediately preceding six months. As such, the onset of increased libido did not occur until the patient had been taking tamoxifen for about four months. Moreover, when the patient was reevaluated in January of 1995, his libido had returned to normal levels despite the fact that he continued tamoxifen treatment. Thus, the perceived side effect of increased libido was not observed until the patient had been on tamoxifen for a relatively long time, and it resolved before the patient discontinued his tamoxifen treatment.

Further, as discussed above, Delaney *et al.* do not report that any studies were conducted to determine whether the tamoxifen treatment was definitively linked to the patient's increase in libido, and did not attempt to establish whether the increased libido might have been linked to any of the other treatments to which the cancer patient had been subjected, including chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil, as well as radiotherapy. Instead, the authors of Delaney *et al.* were unsure as to the cause of the increased libido. They do not disclose any evidence that tamoxifen treatment and increased libido were causatively linked.

In addition, as discussed above, Delaney *et al.* disclose that the increase in libido observed in this one patient was contrary to other case reports in which tamoxifen therapy was associated with impotence, and that previous studies had found that 5 to 30 percent of men receiving tamoxifen experienced reduced libido. Thus, Delaney *et al.* clearly teaches that the patient in question was an outlier, and that tamoxifen treatment would be expected to reduce libido rather than to increase libido.

Moreover, libido and modulation of penile vascular tone are significantly different conditions; modulation of penile vascular tone cannot be equated with an increase in libido. Thus, even if tamoxifen treatment was casually linked to increased libido, there would have been no reason to believe that it could be used to modulate penile vascular tone. A modulation in penile vascular tone and increased libido are distinct and cannot be equated.

In summary, given the differences between libido and the modulation of penile vascular tone, together with the lack of evidence establishing that tamoxifen treatment was causally associated with one individual's increased libido, as well as the failure of Delaney *et al.* to

disclose that tamoxifen would be useful in a patient in need of the modulation of penile vascular tone, it is clear that the cited documents do not anticipate claim 34.

Claim 35

Claim 35 recites the method of claim 34 (*i.e.*, a method to modulate penile vascular tone in a male mammal in need thereof, said method comprising administering a pharmaceutically effective amount of a chloride channel blocking agent, or a pharmaceutically acceptable salt thereof), wherein the chloride channel blocking agent is a compound of Formula I), wherein the compound administered is 1-p-β-dimethylaminoethoxyphenyl-trans-l, 2-diphenylbut-1-ene, or a pharmaceutically acceptable salt thereof.

Applicants respectfully assert that Delaney *et al.* fails to anticipate claim 35. As discussed above, Delaney *et al.* discloses that one male patient on a tamoxifen regimen had experienced increased libido during a portion of his course of treatment. At no point do Delaney *et al.* disclose that the patient had a need for the modulation of penile vascular tone, as recited in claim 35. Delaney *et al.* fails to suggest that tamoxifen might be useful to modulate penile vascular tone in a patient in need thereof. Further, as discussed above, Delaney *et al.* fail to establish a causative link between tamoxifen treatment and increased libido.

Delaney *et al.* disclose that one male cancer patient experienced increased libido during a course of treatment with tamoxifen. According to Delaney *et al.*, the patient began tamoxifen treatment in April of 1993. Ten months later, in February of 1994, he reported that he had experienced significantly enhanced libido for the immediately preceding six months. As such, the onset of increased libido did not occur until the patient had been taking tamoxifen for about four months. Moreover, when the patient was reevaluated in January of 1995, his libido had returned to normal levels despite the fact that he continued tamoxifen treatment. Thus, the perceived side effect of increased libido was not observed until the patient had been on tamoxifen for a relatively long time, and it resolved before the patient discontinued his tamoxifen treatment.

Further, as discussed above, Delaney *et al.* do not report that any studies were conducted to determine whether the tamoxifen treatment was definitively linked to the patient's increase in libido, and did not attempt to establish whether the increased libido might have been linked to

any of the other treatments to which the cancer patient had been subjected, including chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil, as well as radiotherapy. Instead, the authors of Delaney *et al.* were unsure as to the cause of the increased libido. They do not disclose any evidence that tamoxifen treatment and increased libido were causatively linked.

In addition, as discussed above, Delaney *et al.* disclose that the increase in libido observed in this one patient was contrary to other case reports in which tamoxifen therapy was associated with impotence, and that previous studies had found that 5 to 30 percent of men receiving tamoxifen experienced reduced libido. Thus, Delaney *et al.* clearly teaches that the patient in question was an outlier, and that tamoxifen treatment would be expected to reduce libido rather than to increase libido.

Moreover, as discussed above, libido and erectile dysfunction are significantly different conditions; an improvement in erectile function cannot be equated with an increase in libido. Thus, even if tamoxifen treatment was casually linked to increased libido, there would have been no reason to believe that it could be used to modulate penile vascular tone or to treat erectile dysfunction. Improved erectile function and increased libido are distinct and cannot be equated.

In summary, given the differences between libido and the modulation of penile vascular tone, together with the lack of evidence establishing that tamoxifen treatment was causally associated with one individual's increased libido, as well as the failure of Delaney *et al.* to disclose that tamoxifen would be useful in a patient in need of the modulation of penile vascular tone, it is clear that the cited documents do not anticipate claim 35.

Claim 39

Claim 39 recites a method of claim 33 (*i.e.*, a method to modulate penile vascular tone in a male mammal in need thereof, said method comprising administering a pharmaceutically effective amount of a chloride channel blocking agent, or a pharmaceutically acceptable salt thereof), wherein the chloride channel is a CLC3 channel.

Applicants respectfully assert that Delaney *et al.* fails to anticipate claim 39. As discussed above, Delaney *et al.* discloses that one male patient on a tamoxifen regimen had experienced increased libido during a portion of his course of treatment. At no point do Delaney

et al. disclose that the patient had a need for the modulation of penile vascular tone, as recited in claim 39. Delaney *et al.* fails to suggest that tamoxifen might be useful to modulate penile vascular tone in a patient in need thereof. Further, as discussed above, Delaney *et al.* fail to establish a causative link between tamoxifen treatment and increased libido.

Delaney *et al.* disclose that one male cancer patient experienced increased libido during a course of treatment with tamoxifen. According to Delaney *et al.*, the patient began tamoxifen treatment in April of 1993. Ten months later, in February of 1994, he reported that he had experienced significantly enhanced libido for the immediately preceding six months. As such, the onset of increased libido did not occur until the patient had been taking tamoxifen for about four months. Moreover, when the patient was reevaluated in January of 1995, his libido had returned to normal levels despite the fact that he continued tamoxifen treatment. Thus, the perceived side effect of increased libido was not observed until the patient had been on tamoxifen for a relatively long time, and it resolved before the patient discontinued his tamoxifen treatment.

Further, as discussed above, Delaney *et al.* do not report that any studies were conducted to determine whether the tamoxifen treatment was definitively linked to the patient's increase in libido, and did not attempt to establish whether the increased libido might have been linked to any of the other treatments to which the cancer patient had been subjected, including chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil, as well as radiotherapy. Instead, the authors of Delaney *et al.* were unsure as to the cause of the increased libido. They do not disclose any evidence that tamoxifen treatment and increased libido were causatively linked.

In addition, as discussed above, Delaney *et al.* disclose that the increase in libido observed in this one patient was contrary to other case reports in which tamoxifen therapy was associated with impotence, and that previous studies had found that 5 to 30 percent of men receiving tamoxifen experienced reduced libido. Thus, Delaney *et al.* clearly teaches that the patient in question was an outlier, and that tamoxifen treatment would be expected to reduce libido rather than to increase libido.

Moreover, as discussed above, libido and modulation of penile vascular tone are significantly different conditions; a modulation of penile vascular tone cannot be equated with an

increase in libido. Thus, even if tamoxifen treatment was casually linked to increased libido, there would have been no reason to believe that it could be used to modulate penile vascular tone. Improved erectile function and increased libido are distinct and cannot be equated.

In summary, given the differences between libido and the modulation of penile vascular tone, together with the lack of evidence establishing that tamoxifen treatment was causally associated with one individual's increased libido, as well as the failure of Delaney *et al.* to disclose that tamoxifen would be useful in a patient in need of the modulation of penile vascular tone, it is clear that the cited documents do not anticipate claim 39.

Claim 40

Claim 40 recites the method of claim 39 (*i.e.*, a method to modulate penile vascular tone in a male mammal in need thereof, said method comprising administering a pharmaceutically effective amount of a chloride channel blocking agent, or a pharmaceutically acceptable salt thereof), wherein the chloride channel is a CLC3 channel), wherein blocking the CLC3 channel results in diminished vasoconstriction to norepinephrine.

Applicants respectfully assert that Delaney *et al.* fails to anticipate claim 40. As discussed above, Delaney *et al.* discloses that one male patient on a tamoxifen regimen had experienced increased libido during a portion of his course of treatment. At no point do Delaney *et al.* disclose that the patient had a need for the modulation of penile vascular tone wherein blocking the CLC3 channel results in diminished vasoconstriction to norepinephrine, as recited in claim 40. Delaney *et al.* fails to suggest that tamoxifen might be useful to modulate penile vascular tone in a patient in need thereof. Further, as discussed above, Delaney *et al.* fail to establish a causative link between tamoxifen treatment and increased libido.

Delaney *et al.* disclose that one male cancer patient experienced increased libido during a course of treatment with tamoxifen. According to Delaney *et al.*, the patient began tamoxifen treatment in April of 1993. Ten months later, in February of 1994, he reported that he had experienced significantly enhanced libido for the immediately preceding six months. As such, the onset of increased libido did not occur until the patient had been taking tamoxifen for about four months. Moreover, when the patient was reevaluated in January of 1995, his libido had returned to normal levels despite the fact that he continued tamoxifen treatment. Thus, the

perceived side effect of increased libido was not observed until the patient had been on tamoxifen for a relatively long time, and it resolved before the patient discontinued his tamoxifen treatment.

Further, as discussed above, Delaney *et al.* do not report that any studies were conducted to determine whether the tamoxifen treatment was definitively linked to the patient's increase in libido, and did not attempt to establish whether the increased libido might have been linked to any of the other treatments to which the cancer patient had been subjected, including chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil, as well as radiotherapy. Instead, the authors of Delaney *et al.* were unsure as to the cause of the increased libido. They do not disclose any evidence that tamoxifen treatment and increased libido were causatively linked.

In addition, as discussed above, Delaney *et al.* disclose that the increase in libido observed in this one patient was contrary to other case reports in which tamoxifen therapy was associated with impotence, and that previous studies had found that 5 to 30 percent of men receiving tamoxifen experienced reduced libido. Thus, Delaney *et al.* clearly teaches that the patient in question was an outlier, and that tamoxifen treatment would be expected to reduce libido rather than to increase libido.

Moreover, libido and modulation of penile vascular tone are significantly different conditions; a modulation in penile vascular tone cannot be equated with an increase in libido. Thus, even if tamoxifen treatment was casually linked to increased libido, there would have been no reason to believe that it could be used to modulate penile vascular tone, wherein blocking a CLC3 channel results in diminished vasoconstriction to norepinephrine.

In summary, given the differences between libido and the modulation of penile vascular tone, together with the lack of evidence establishing that tamoxifen treatment was causally associated with one individual's increased libido, as well as the failure of Delaney *et al.* to disclose that tamoxifen would be useful in a patient in need of the modulation of penile vascular tone, it is clear that the cited documents do not anticipate claim 40.

Claim 41

Claim 41 recites the method of claim 39 (*i.e.*, a method to modulate penile vascular tone in a male mammal in need thereof, said method comprising administering a pharmaceutically effective amount of a chloride channel blocking agent, or a pharmaceutically acceptable salt thereof), wherein the chloride channel is a CLC3 channel), wherein blocking the CLC3 channel reduces penile sympathetic tone.

Applicants respectfully assert that Delaney *et al.* fails to anticipate claim 41. As discussed above, Delaney *et al.* discloses that one male patient on a tamoxifen regimen had experienced increased libido during a portion of his course of treatment. At no point do Delaney *et al.* disclose that the patient had a need for the modulation of penile vascular tone, wherein blocking a CLC3 channel reduces penile sympathetic tone, as recited in claim 41. Delaney *et al.* fails to suggest that tamoxifen might be useful to modulate penile vascular tone in a patient in need thereof. Further, as discussed above, Delaney *et al.* fail to establish a causative link between tamoxifen treatment and increased libido.

Delaney *et al.* disclose that one male cancer patient experienced increased libido during a course of treatment with tamoxifen. According to Delaney *et al.*, the patient began tamoxifen treatment in April of 1993. Ten months later, in February of 1994, he reported that he had experienced significantly enhanced libido for the immediately preceding six months. As such, the onset of increased libido did not occur until the patient had been taking tamoxifen for about four months. Moreover, when the patient was reevaluated in January of 1995, his libido had returned to normal levels despite the fact that he continued tamoxifen treatment. Thus, the perceived side effect of increased libido was not observed until the patient had been on tamoxifen for a relatively long time, and it resolved before the patient discontinued his tamoxifen treatment.

Further, as discussed above, Delaney *et al.* do not report that any studies were conducted to determine whether the tamoxifen treatment was definitively linked to the patient's increase in libido, and did not attempt to establish whether the increased libido might have been linked to any of the other treatments to which the cancer patient had been subjected, including chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil, as well as radiotherapy. Instead, the authors of Delaney *et al.* were unsure as to the cause of the increased libido. They

do not disclose any evidence that tamoxifen treatment and increased libido were causatively linked.

In addition, as discussed above, Delaney *et al.* disclose that the increase in libido observed in this one patient was contrary to other case reports in which tamoxifen therapy was associated with impotence, and that previous studies had found that 5 to 30 percent of men receiving tamoxifen experienced reduced libido. Thus, Delaney *et al.* clearly teaches that the patient in question was an outlier, and that tamoxifen treatment would be expected to reduce libido rather than to increase libido.

Moreover, as discussed above, libido and modulation of penile vascular tone are significantly different conditions; a modulation in penile vascular tone cannot be equated with an increase in libido. Thus, even if tamoxifen treatment was casually linked to increased libido, there would have been no reason to believe that it could be used to modulate penile vascular tone.

In summary, given the differences between libido and the modulation of penile vascular tone, together with the lack of evidence establishing that tamoxifen treatment was causally associated with one individual's increased libido, as well as the failure of Delaney *et al.* to disclose that tamoxifen would be useful in a patient in need of the modulation of penile vascular tone, it is clear that the cited documents do not anticipate claim 41.

Claim 42

Claim 42 recites the method of claim 41 (*i.e.*, a method to modulate penile vascular tone in a male mammal in need thereof, said method comprising administering a pharmaceutically effective amount of a chloride channel blocking agent, or a pharmaceutically acceptable salt thereof), wherein the chloride channel is a CLC3 channel), wherein blocking the CLC3 channel reduces penile sympathetic tone), wherein the reduction of penile sympathetic tone induces an erection.

Applicants respectfully assert that Delaney *et al.* fails to anticipate claim 42. As discussed above, Delaney *et al.* discloses that one male patient on a tamoxifen regimen had experienced increased libido during a portion of his course of treatment. At no point do Delaney *et al.* disclose that the patient had a need for the modulation of penile vascular tone, as recited in

claim 42. Delaney *et al.* fails to suggest that tamoxifen might be useful to modulate penile vascular tone in a patient in need thereof. Further, as discussed above, Delaney *et al.* fail to establish a causative link between tamoxifen treatment and increased libido.

Delaney *et al.* disclose that one male cancer patient experienced increased libido during a course of treatment with tamoxifen. According to Delaney *et al.*, the patient began tamoxifen treatment in April of 1993. Ten months later, in February of 1994, he reported that he had experienced significantly enhanced libido for the immediately preceding six months. As such, the onset of increased libido did not occur until the patient had been taking tamoxifen for about four months. Moreover, when the patient was reevaluated in January of 1995, his libido had returned to normal levels despite the fact that he continued tamoxifen treatment. Thus, the perceived side effect of increased libido was not observed until the patient had been on tamoxifen for a relatively long time, and it resolved before the patient discontinued his tamoxifen treatment.

Further, as discussed above, Delaney *et al.* do not report that any studies were conducted to determine whether the tamoxifen treatment was definitively linked to the patient's increase in libido, and did not attempt to establish whether the increased libido might have been linked to any of the other treatments to which the cancer patient had been subjected, including chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil, as well as radiotherapy. Instead, the authors of Delaney *et al.* were unsure as to the cause of the increased libido. They do not disclose any evidence that tamoxifen treatment and increased libido were causatively linked.

In addition, as discussed above, Delaney *et al.* disclose that the increase in libido observed in this one patient was contrary to other case reports in which tamoxifen therapy was associated with impotence, and that previous studies had found that 5 to 30 percent of men receiving tamoxifen experienced reduced libido. Thus, Delaney *et al.* clearly teaches that the patient in question was an outlier, and that tamoxifen treatment would be expected to reduce libido rather than to increase libido.

Moreover, as discussed above, libido and erectile dysfunction are significantly different conditions; an improvement in erectile function cannot be equated with an increase in libido. Thus, even if tamoxifen treatment was casually linked to increased libido, there would have been

no reason to believe that it could be used to modulate penile vascular tone or to treat erectile dysfunction. Improved erectile function and increased libido are distinct and cannot be equated.

In summary, given the differences between libido and the modulation of penile vascular tone, together with the lack of evidence establishing that tamoxifen treatment was causally associated with one individual's increased libido, as well as the failure of Delaney *et al.* to disclose that tamoxifen would be useful in a patient in need of the modulation of penile vascular tone, it is clear that the cited documents do not anticipate claim 42.

Claim 43

Independent claim 43 recites a method for treating erectile dysfunction in a male patient comprising administering to the male patient a composition comprising a CLC3 channel blocking agent or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Applicants respectfully assert that Delaney *et al.* fails to anticipate claim 43. As discussed above, Delaney *et al.* discloses that one male patient on a tamoxifen regimen had experienced increased libido during his course of treatment. At no point do Delaney *et al.* disclose that the patient had compromised vascular tissue associated with erectile dysfunction, as recited in claim 43. As discussed above, Delaney *et al.* fails to suggest that tamoxifen might be useful to modulate penile vascular tone in a patient with erectile dysfunction. Further, as discussed above, Delaney *et al.* fail to establish a causative link between tamoxifen treatment and increased libido.

Delaney *et al.* disclose that one male cancer patient experienced increased libido during a course of treatment with tamoxifen. According to Delaney *et al.*, the patient began tamoxifen treatment in April of 1993. Ten months later, in February of 1994, he reported that he had experienced significantly enhanced libido for the immediately preceding six months. As such, the onset of increased libido did not occur until the patient had been taking tamoxifen for about four months. Moreover, when the patient was reevaluated in January of 1995, his libido had returned to normal levels despite the fact that he continued tamoxifen treatment. Thus, the perceived side effect of increased libido was not observed until the patient had been on

tamoxifen for a relatively long time, and it resolved before the patient discontinued his tamoxifen treatment.

Further, as discussed above, Delaney *et al.* do not report that any studies were conducted to determine whether the tamoxifen treatment was definitively linked to the patient's increase in libido, and did not attempt to establish whether the increased libido might have been linked to any of the other treatments to which the cancer patient had been subjected, including chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil, as well as radiotherapy. Instead, the authors of Delaney *et al.* were unsure as to the cause of the increased libido. They do not disclose any evidence that tamoxifen treatment and increased libido were causatively linked.

In addition, as discussed above, Delaney *et al.* disclose that the increase in libido observed in this one patient was contrary to other case reports in which tamoxifen therapy was associated with impotence, and that previous studies had found that 5 to 30 percent of men receiving tamoxifen experienced reduced libido. Thus, Delaney *et al.* clearly teaches that the patient in question was an outlier, and that tamoxifen treatment would be expected to reduce libido rather than to increase libido.

Moreover, as discussed above, libido and erectile dysfunction are significantly different conditions; an improvement in erectile function cannot be equated with an increase in libido. Thus, even if tamoxifen treatment was casually linked to increased libido, there would have been no reason to believe that it could be used to modulate penile vascular tone or to treat erectile dysfunction. Improved erectile function and increased libido are distinct and cannot be equated.

In summary, given the differences between libido and erectile dysfunction, together with the lack of evidence establishing that tamoxifen treatment was causally associated with one individual's increased libido, as well as the failure of Delaney *et al.* to disclose that tamoxifen would be useful in a patient having compromised vascular tissue and/or erectile dysfunction, it is clear that the cited documents do not anticipate claim 43.

Conclusion

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claims 22-24, 27-29, 33-35, and 39-43 under 35 U.S.C. § 102(b).

B. The Claims Are Patentable over Delaney *et al.* in View of the Zhang *et al.* Patent and Drug Facts and Comparisons (1997)

The Examiner alleges that claims 31, 32 and 38 are unpatentable over Delaney *et al.* as applied to claims 22-24, 27-29, 33-35, and 39-43, and further in view of the Zhang *et al.* patent and *Drug Facts and Comparisons* (1997). The Examiner stated that while Delaney *et al.* does not expressly teach the route of administration set forth in claims 32 and 38, or the further administration of the agents set forth in claim 31, *Drug Facts and Comparisons* teaches that tamoxifen is commercially available in oral form, while the Zhang *et al.* patent reports that vasodilators are useful for treatment of erectile dysfunction. Thus, the Examiner concluded that it would have been obvious to a person having ordinary skill in the art to administer tamoxifen orally. The Examiner also concluded that it would have been obvious to incorporate a vasodilator agent with tamoxifen because vasodilators are useful for treatment of erectile dysfunction.

Claim 31

Claim 31 recites the method of claim 22 (*i.e.*, a method to modulate vascular tone in a male patient having compromised vascular tissue associated with erectile dysfunction, comprising administering to the male patient a pharmaceutically effective amount of a chloride channel blocking agent, or a pharmaceutically acceptable salt thereof), further comprising administering a pharmaceutically effective compound selected from an anti-diabetes agent, an anti-hypertension agent, an anti-coronary artery disease agent, an anti-restenosis agent, and a vasodilatory agent.

As discussed above, Delaney *et al.* discloses only that one male patient experienced increased libido during a portion of the time for which he was on a tamoxifen regimen. The patient was disclosed to be a 35 year-old breast cancer patient. At no point was he disclosed to have erectile dysfunction or to be in need of modulated penile vascular tone. Thus, Delaney *et al.* fails to provide any suggestion that tamoxifen might be useful to modulate vascular tone in a patient having compromised vascular tissue.

Moreover, Delaney *et al.* teaches away from using tamoxifen to increase libido. In fact, Delaney *et al.* teach that tamoxifen treatment is more likely to result in reduced libido than

increased libido. In addition, libido and erectile function are very different conditions, as described above. Even if libido and erectile dysfunction could be equated, which they cannot, a subject having erectile dysfunction or compromised penile vascular tissue surely would not have been motivated by Delaney *et al.* to use tamoxifen to treat his condition. This is particularly true given the four-month lag time between administration of tamoxifen and the reported onset of increased libido, as well as the reduction in libido to normal levels prior to discontinuation of tamoxifen therapy. As such, a person of ordinary skill in the art reading Delaney *et al.* would not have been motivated to use a chloride channel blocking agent such as tamoxifen to modulate vascular tone in a patient, or to modulate penile vascular tone in a mammal in need thereof.

The Zhang *et al.* patent and the Drug Facts and Comparisons document fail to remedy the deficiencies of Delaney *et al.*. At no point do either of these documents suggest that a chloride channel blocking agent such as tamoxifen would be useful either to modulate vascular tone in a patient having compromised vascular tissue associated with erectile dysfunction or to modulate penile vascular tone in a mammal in need thereof. Moreover, at no point does the combination of Delaney *et al.* with the Zhang *et al.* patent and the Drug Facts and Comparisons document suggest that a chloride channel blocker would be useful to modulate vascular tone either alone or in combination with another agent (*e.g.*, a vasodilator), regardless of how it was administered. Thus, the combination of these three documents fails to render claim 31 obvious.

Claim 32

Claim 32 recites the method of claim 22 (*i.e.*, a method to modulate vascular tone in a male patient having compromised vascular tissue associated with erectile dysfunction, comprising administering to the male patient a pharmaceutically effective amount of a chloride channel blocking agent, or a pharmaceutically acceptable salt thereof), wherein the agent is administered intravenously or orally.

As discussed above, Delaney *et al.* discloses only that one male patient experienced increased libido during a portion of the time for which he was on a tamoxifen regimen. The patient was disclosed to be a 35 year-old breast cancer patient. At no point was he disclosed to have erectile dysfunction or to be in need of modulated penile vascular tone. Thus, Delaney *et*

al. fails to provide any suggestion that tamoxifen might be useful to modulate vascular tone in a patient having compromised vascular tissue.

Moreover, Delaney *et al.* teaches away from using tamoxifen to increase libido. In fact, Delaney *et al.* teach that tamoxifen treatment is more likely to result in reduced libido than increased libido. In addition, libido and erectile function are very different conditions, as described above. Even if libido and erectile dysfunction could be equated, which they cannot, a subject having erectile dysfunction or compromised penile vascular tissue surely would not have been motivated by Delaney *et al.* to use tamoxifen to treat his condition. This is particularly true given the four-month lag time between administration of tamoxifen and the reported onset of increased libido, as well as the reduction in libido to normal levels prior to discontinuation of tamoxifen therapy. As such, a person of ordinary skill in the art reading Delaney *et al.* would not have been motivated to use a chloride channel blocking agent such as tamoxifen to modulate vascular tone in a patient, or to modulate penile vascular tone in a mammal in need thereof.

The Zhang *et al.* patent and the Drug Facts and Comparisons document fail to remedy the deficiencies of Delaney *et al.*. At no point do either of these documents suggest that a chloride channel blocking agent such as tamoxifen would be useful either to modulate vascular tone in a patient having compromised vascular tissue associated with erectile dysfunction or to modulate penile vascular tone in a mammal in need thereof. Moreover, at no point does the combination of Delaney *et al.* with the Zhang *et al.* patent and the Drug Facts and Comparisons document suggest that a chloride channel blocker would be useful to modulate vascular tone either alone or in combination with another agent (*e.g.*, a vasodilator), regardless of how it was administered. Thus, the combination of these three documents fails to render claim 32 obvious.

Claim 38

Claim 38 recites the method of claim 33 (*i.e.*, a method to modulate penile vascular tone in a male mammal in need thereof, said method comprising administering a pharmaceutically effective amount of a chloride channel blocking agent, or a pharmaceutically acceptable salt thereof), wherein the agent is administered orally or intravenously.

As discussed above, Delaney *et al.* discloses only that one male patient experienced increased libido during a portion of the time for which he was on a tamoxifen regimen. The

patient was disclosed to be a 35 year-old breast cancer patient. At no point was he disclosed to have erectile dysfunction or to be in need of modulated penile vascular tone. Thus, Delaney *et al.* fails to provide any suggestion that tamoxifen might be useful to modulate vascular tone in a patient having compromised vascular tissue.

Moreover, Delaney *et al.* teaches away from using tamoxifen to increase libido. In fact, Delaney *et al.* teach that tamoxifen treatment is more likely to result in reduced libido than increased libido. In addition, libido and erectile function are very different conditions, as described above. Even if libido and erectile dysfunction could be equated, which they cannot, a subject having erectile dysfunction or compromised penile vascular tissue surely would not have been motivated by Delaney *et al.* to use tamoxifen to treat his condition. This is particularly true given the four-month lag time between administration of tamoxifen and the reported onset of increased libido, as well as the reduction in libido to normal levels prior to discontinuation of tamoxifen therapy. As such, a person of ordinary skill in the art reading Delaney *et al.* would not have been motivated to use a chloride channel blocking agent such as tamoxifen to modulate vascular tone in a patient, or to modulate penile vascular tone in a mammal in need thereof.

The Zhang *et al.* patent and the Drug Facts and Comparisons document fail to remedy the deficiencies of Delaney *et al.*. At no point do either of these documents suggest that a chloride channel blocking agent such as tamoxifen would be useful either to modulate vascular tone in a patient having compromised vascular tissue associated with erectile dysfunction or to modulate penile vascular tone in a mammal in need thereof. Moreover, at no point does the combination of Delaney *et al.* with the Zhang *et al.* patent and the Drug Facts and Comparisons document suggest that a chloride channel blocker would be useful to modulate vascular tone either alone or in combination with another agent (*e.g.*, a vasodilator), regardless of how it was administered. Thus, the combination of these three documents fails to render claim 38 obvious.

Conclusion

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claims 31, 32, and 38 under 35 U.S.C. § 103(a).

Respectfully submitted,

Fred S. Lamb et al.

By their Representatives,

Viksnins Harris & Padys PLLP
Customer Number 53137
PO Box 111098
St. Paul, MN 55111-1098
(952) 876-4091

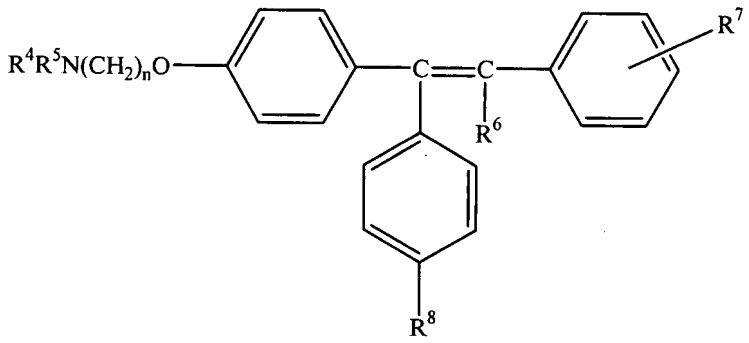
Date: May 30, 2007

By: Ann S. Viksnins
Ann S. Viksnins
Reg. No. 37,748

(8) Claims Appendix.

22. A method to modulate vascular tone in a male patient having compromised vascular tissue associated with erectile dysfunction, comprising administering to the male patient a pharmaceutically effective amount of a chloride channel blocking agent, or a pharmaceutically acceptable salt thereof.

23. A method of claim 22, wherein the chloride channel blocking agent is a compound of Formula I



I

wherein either R^4 is H or a lower alkyl radical and R^5 is a lower alkyl radical, or R^4 and R^5 are joined together with the adjacent nitrogen atom to form a heterocyclic radical;

R^6 is H or a lower alkyl radical;

R^7 is H, halo, OH, a lower alkyl radical, or is a buta-1,3-dienyl radical which together with the adjacent benzene ring forms a naphthyl radical;

R^8 is H or OH; and

n is 2;

or a pharmaceutically acceptable salt thereof.

24. A method of claim 23, wherein the compound is 1-p-β-dimethylaminoethoxyphenyl-trans-1,2-diphenylbut-1-ene, or a pharmaceutically acceptable salt thereof.

27. A method of claim 22, wherein the chloride channel is a CLC3 channel.

28. The method of claim 27, wherein blocking the CLC3 channel results in diminished vasoconstriction to norepinephrine.

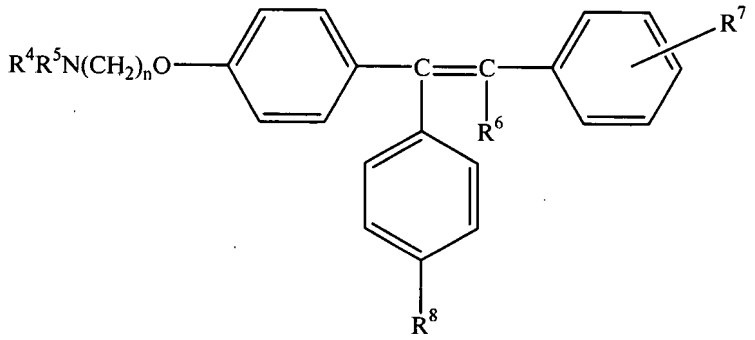
29. The method of claim 22, wherein the agent modulates vascular tone by enhancing vasodilation.

31. A method of claim 22, further comprising administering a pharmaceutically effective compound selected from an anti-diabetes agent, an anti-hypertension agent, an anti-coronary artery disease agent, an anti-restenosis agent, and a vasodilatory agent.

32. A method of claim 22, wherein the agent is administered intravenously or orally.

33. A method to modulate penile vascular tone in a male mammal in need thereof, said method comprising administering a pharmaceutically effective amount of a chloride channel blocking agent, or a pharmaceutically acceptable salt thereof.

34. A method of claim 33, wherein the chloride channel blocking agent is a compound of Formula I



I

wherein either R^4 is H or a lower alkyl radical and R^5 is a lower alkyl radical, or R^4 and R^5 are joined together with the adjacent nitrogen atom to form a heterocyclic radical;

R^6 is H or a lower alkyl radical;

R^7 is H, halo, OH, a lower alkyl radical, or is a buta-1,3-dienyl radical which together with the adjacent benzene ring forms a naphthyl radical;

R^8 is H or OH; and

n is 2;

or a pharmaceutically acceptable salt thereof.

35. A method of claim 34, wherein the compound administered is 1-p-β-dimethylaminoethoxyphenyl-trans-l, 2-diphenylbut-1-ene, or a pharmaceutically acceptable salt thereof.

38. The method of claim 33, wherein the agent is administered orally or intravenously.

39. A method of claim 33, wherein the chloride channel is a CLC3 channel.

40. The method of claim 39, wherein blocking the CLC3 channel results in diminished vasoconstriction to norepinephrine.

41. The method of claim 39, wherein blocking the CLC3 channel reduces penile sympathetic tone.

42. The method of claim 41, wherein the reduction of penile sympathetic tone induces an erection.

43. A method for treating erectile dysfunction in a male patient comprising administering to the male patient a composition comprising a CLC3 channel blocking agent or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

(9) Evidence Appendix.

A. U.S. Patent No. 5,658,936

This document was entered by the Examiner in the Office Action mailed August 24, 2004.

B. U.S. Patent No. 6,266,560

This document was entered by the Examiner in the Office Action mailed August 24, 2004.

C. Delaney *et al.* (Delaney *et al.*, (1996) *The Breast* 5:53-54)

This document was entered by the Examiner in the Office Action mailed August 24, 2004.

D. Drug Facts and Comparisons (1997)

This document was entered by the Examiner in the Office Action mailed August 24, 2004.

E. "Erectile dysfunction" definition, the On-Line Medical Dictionary

This document was submitted with the Amendment and Reply filed November 2, 2004, which the Examiner indicated will be entered for the purposes of appeal in the Advisory Action mailed November 26, 2004.

F. "Libido" definition, the Merriam-Webster online dictionary

This document was submitted with the Amendment and Reply filed November 2, 2004, which the Examiner indicated will be entered for the purposes of appeal in the Advisory Action mailed November 26, 2004.

(10) Related Proceedings Appendix.

There have been no decisions rendered by a court or the Board in the appeal of Application Serial No. 09/512,926.

The Breast (1996) 5, 53–54

CASE REPORT

Increased libido: a complication of tamoxifen therapy of male breast cancer

G. P. Delaney and A. O. Langlands

Division of Radiation Oncology, Westmead Hospital, Westmead, Australia

SUMMARY. This is a clinical report of a male patient with breast cancer who developed the unusual side-effect of significantly increased libido when commenced on tamoxifen.

CASE REPORT

A 35-year-old man was first referred in October 1988 after undergoing a modified radical mastectomy of the right breast. The histopathology showed a 3 cm × 3 cm infiltrating ductal carcinoma; foci of lymphatic invasion were present and four of 35 axillary lymph nodes were involved. Oestrogen receptor status was not known. Six cycles of adjuvant CMF (cyclophosphamide, methotrexate, 5-fluorouracil) were given with minimal toxicity. In June 1992 he returned with multiple bone metastases. As his pain was well controlled he received no active treatment until February 1993 when he was given palliative radiotherapy to the thoracic spine. Tamoxifen 20 mg daily was commenced in April 1993.

In February 1994, the patient was seen for review. At that time his pain was well controlled. He complained of two side-effects since commencement of tamoxifen – the development of an acneform rash and for the immediately preceding 6 months significantly enhanced libido including nocturnal emissions. Tamoxifen was continued. At his last assessment in January 1995, he had reported that his libido had returned to normal and his rash had resolved. Serial serum hormones were obtained (Table). These showed elevation of luteinizing hormone (LH) and follicular stimulating hormone (FSH) and maintenance of testosterone levels within normal levels.

Address correspondence to: G. P. Delaney, Division of Radiation Oncology, Westmead Hospital, Darcy Road, Westmead NSW 2145, Australia

Table Hormone levels

Hormone	Normal range	2/1994	11/1994	1/1995
FSH	< 8.7 IU/L	11	42.3	45.1
LH	< 9.0 IU/L	13.7	20.8	27.1
Testosterone	12–36 nmol/L	23.0	12.0	17.0
Oestradiol	40–160 pmol/L	ND	102	172
Prolactin	< 495 miu/L	ND	120	191

ND = not done.

DISCUSSION

In premenopausal women tamoxifen causes elevation of serum oestrogen and progesterone and major changes in FSH and LH do not occur. In postmenopausal women the normally elevated levels of gonadotrophins decrease and testosterone, oestrogen and progesterone remain largely unchanged.[1] The hormone profile in men is less clear. In infertile men, a randomized study found statistically significant increases in serum testosterone, FSH, LH and oestradiol but no changes in serum prolactin in the men taking tamoxifen.[2] This finding is in contrast to recent case reports indicating that impotence secondary to tamoxifen therapy was associated with castration levels of testosterone and that this clinical effect was reversed following withdrawal of tamoxifen.[3] In this case report our patient's testosterone level remained within normal limits. In our patient an initial mild elevation in FSH and LH resulted in no change in testosterone but was clinically manifest as heightened libido. With further tamoxifen therapy the FSH and LH increased further, but the patient's libido has returned to normal and testosterone has remained within normal limits. We are not aware of any previous reports of increased libido as a potential side-effect of tamoxifen, on the contrary, 5–30% of men receiving tamoxifen experience reduced libido.[4,5] Approximately 50%

of women report loss of libido as a significant clinical problem.[1] This patient is significantly younger than most men taking tamoxifen for metastatic breast cancer and perhaps this side-effect may be related to the patient's young age.

References

1. Love R R. Tamoxifen therapy in primary breast cancer: biology, efficacy and side effects. J Clin Oncol 1989; 7: 803–815.
2. Ain Melk Y, Belisle S, Carmel M, Tetreault J P. Tamoxifen citrate therapy in male infertility. Fertility and Sterility 1987; 48(1): 113–117.
3. Collinson M P, Hamilton D A, Tyrell C J. Two case reports of tamoxifen as a cause of impotence in male subjects with carcinoma of the breast. Breast 1993; 2: 48–49.
4. Annelli T F, Annelli A, Tran K N, Leibwohl D E, Borgen P I. Tamoxifen administration is associated with a high rate of treatment – limiting symptoms in male breast cancer patients. Cancer 1994; 74: 74–77.
5. Ralph D J, Brooks M D, Bottazzo E K, Pryor J P. The treatment of Peyronie's disease with tamoxifen. Br J Urol 1992; 70: 648–651.

drug facts and comparisons®

1997 edition

Antiestrogen

TAMOXIFEN CITRATE

Tamoxifen vs Ovarian Ablation: Adverse Reactions (%)		
Adverse reactions	Tamoxifen (n = 104)	Ovarian ablation (n = 100)
Flushing	32.7	46
Amenorrhea	16.3	69
Altered menses	12.5	5
Oligomenorrhea	8.7	1
Bone pain	5.7	6
Menstrual disorder	5.7	4
Nausea	4.8	4
Coughing	3.8	1
Edema	3.8	1
Fatigue	3.8	1
Musculoskeletal pain	2.8	0
Pain	2.8	4
Ovarian cyst(s)	2.8	2
Depression	1.9	2
Abdominal cramps	1	2
Anorexia	1	2

Males: Tamoxifen is well tolerated in males with breast cancer. The safety profile appears to be similar to that in females. Loss of libido and impotence have resulted in discontinuation of therapy. Also, in oligospermic males treated with tamoxifen, LH, FSH, testosterone and estrogen levels were elevated.

Overdosage:

Symptoms: In animals, respiratory difficulties and convulsions occurred. In advanced metastatic cancer patients receiving loading doses of > 400 mg/m^2, followed by maintenance doses of 150 mg/m^2 twice daily, acute neurotoxicity manifested by tremor, hyperreflexia, unsteady gait and dizziness was noted. Symptoms occurred within 3 to 5 days of beginning therapy and cleared within 2 to 5 days after stopping therapy. The causal relationship to tamoxifen therapy is unknown. Prolongation of the QT interval was also noted in patients given doses > 250 mg/m^2 loading dose followed by 80 mg/m^2 twice daily. Doses given at which neurological symptoms and QT changes occurred were at least 6-fold higher than the maximum recommended dose.

Treatment: Treatment includes usual supportive measures. Refer to General Management of Acute Overdosage.

Patient Information:

Advise women who are receiving or who have previously received tamoxifen to have regular gynecologic examinations and promptly inform their physician of menstrual irregularities, abnormal vaginal bleeding, change in vaginal discharge or pelvic pain or pressure.

Advise women not to become pregnant during therapy. Barrier or nonhormonal contraceptive measures are recommended during treatment if sexually active.

Notify physician if marked weakness, sleepiness, mental confusion, pain/swelling of legs, shortness of breath, blurred vision, bone pain, hot flashes, nausea, vomiting, weight gain, dizziness, headache or loss of appetite occurs.

Administration and Dosage:

10 or 20 mg twice daily (morning and evening) or 20 mg daily.

Some studies have used dosages of 10 mg 2 or 3 times a day for 2 years, and 10 mg twice daily for 5 years. The reduction in recurrence and mortality was greater in those studies that used the drug for ≥ 2 years than in those that used it for < 2 years. There was no indication that doses > 20 mg/day were more effective. However, optimal duration of adjuvant therapy is not known.

Rx	**Nolvadex** (Zeneca)	**Tablets**: 10 mg (as citrate)	(Nolvadex 600). White. In 60s and 250s.	2.8
Rx	**Tamoxifen** (Barr)		In 60s and 250s.	2.6
Rx	**Nolvadex** (Zeneca)	**Tablets**: 20 mg (as citrate)	(Nolvadex 604). White. In 30s.	NA

Gonadotr

LEUPROLIDE ACETATE

Actions:

Pharmacology: Leuprolide, ar naturally occurring gonadot potency than the natural hc sitizes them ; thus, it inhibit in therapeutic doses. After and testicular steroidogene

Advanced prostatic canc luteinizing hormone (LH) ar sient increase in gonadal st estrone and estradiol in pre istration results in decrease reduced to castrate levels. I menopausal levels. These c trate levels of testosterone Leuprolide also inhibits gro of the reproductive organs.

Central precocious pube gonadotropins are reduced reduced to prepubertal leve gonadotropins will allow fo ment. Natural maturation o lowing discontinuation of le

The following physiologi tion of leuprolide acetate in

Skeletal growth – A meas epiphyseal plates will not cl

Organ growth – Reprodu

Menses – If present, will

Pharmacokinetics:

Leuprolide injection has for the treatment of prostati

Depot –

Monthly formulation: F plasma concentration was Nondetectable leuprolide ac chronic use, but testosteron

3 month formulation: F 48.9 ng/ml were seen at 4 h prolide appeared to be relea els during the third week of the 12 week dosing interval. state level, was similar to th

The mean steady-sta administration to healthy m plasma proteins ranged fro

In healthy male volu revealed that the mean syst

Following administra parent and the M-I metaboli

Clinical trials:

Advanced prostatic cance SC to diethylstilbestrol (DES parable after 2 years of trea similar for the 2 groups. In lide depot did not differ fror

In clinical studies with t progression during the first serum prostate specific anti within normal range (≥ 3.99

Endometriosis – Leuprolic rable to danazol 800 mg/day orrhea, dyspareunia, pelvic endometrial implants.

E

erectile dysfunction

A consistent inability to sustain an erection sufficient for sexual intercourse. Also commonaly known as impotence. Medically, the term erectile dysfunction is used to differentiate impotence from other problems that interfere with sexual intercourse (such as lack of sexual desire and problems with ejaculation and orgasm). Impotence usually has a physical cause, such as disease, injury, drug side-effects, or a disorder that impairs blood flow in the penis. Impotence is treatable in all age groups.

(12 Dec 1998)

Previous: Erdheim disease, Erdheim tumour, Erdmann, Erdmann's reagent, erebus, erect, erectile
Next: erectile tissue, erect illumination, erection, erection, penile

Published at the Dept. of Medical Oncology, University of Newcastle upon Tyne

F

HOME
PREMIUM SERVICES
M-WCollegiate.com
M-WUnabridged.com
Britannica.com
Multi-User Licenses
DOWNLOADS
WORD OF THE DAY
WORD GAMES
WORD FOR THE WISE
ONLINE STORE
HELP
Merriam-Webster Inc.
Company Information

Merriam-Webster Online Dictionary

Thesaurus

One entry found for **libido**.

Main Entry: **li·bi·do**
Pronunciation: l&-'bE-(")dO *also* 'li-b&-"dO
Function: *noun*
Inflected Form(s): *plural* **-dos**
Etymology: New Latin *libidin-, libido,* from Latin, desire, lust, from *libEre* to please -- more at LOVE
1 : emotional or psychic energy that in psychoanalytic theory is derived from primitive biological urges and that is usually goal-directed
2 : sexual drive

For **More Information on "libido" go to Britannica.com**

Get the **Top 10 Search Results for "libido"**

Pronunciation Symbols